OIPE
NOV 13 2006
PATENT & TRADEMARK OFFICE

DPW

Docket No.: C1037.70052US00
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Robert L. Bratzler et al.
Serial No.:	10/668,050
Confirmation No.:	1942
Filed:	September 22, 2003
For:	IMMUNOSTIMULATORY NUCLEIC ACIDS AND CANCER MEDICAMENT COMBINATION THERAPY FOR THE TREATMENT OF CANCER
Examiner:	Not Yet Assigned
Art Unit:	1614

Certificate of Mailing Under 37 CFR 1.8(a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service on the date shown below with sufficient postage as First Class Mail, in an envelope addressed to: Mail Stop PGPUB, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: November 9, 2006

Melissa L.B. Lyons

TRANSMITTAL LETTER

Mail Stop PGPUB
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Enclosed are the following items for filing in connection with the above-referenced Patent Application:

1. Request for Corrected Publication
2. Copies of Publication Pages with Corrections Marked in Red Ink

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 23/2825, under Docket No. C1037.70052US00. A duplicate copy of this paper is enclosed.

Dated: November 9, 2006

Respectfully submitted,

By Pat RH Wall

Patrick R.H. Waller
Registration No.: 41,418
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
(617) 646-8000

OIPE
NOV 13 2006
PATENT & TRADEMARK OFFICE

DOCKET NO.: C1037.70052US00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Robert L. Bratzler et al.
Serial No.:	10/668,050
Confirmation No.:	1942
Filed:	September 22, 2003
For:	IMMUNOSTIMULATORY NUCLEIC ACIDS AND CANCER MEDICAMENT COMBINATION THERAPY FOR THE TREATMENT OF CANCER
Examiner:	Not Yet Assigned
Art Unit:	1614

Certificate of Mailing Under 37 CFR 1.8(a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service on the date shown below with sufficient postage as First Class Mail, in an envelope addressed to: Mail Stop PGPUB, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: November 9, 2006

Pat L H Waller

Patrick R.H. Waller

MAIL STOP PGPUB
Commissioner For Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CORRECTED PUBLICATION

Sir:

Applicant in the above-referenced application respectfully requests correction of the corresponding published application US-2006-0211639-A1, published on September 21, 2006.

The published version of the application, page 1, column 1, paragraph 5, line 5, reads "example, surgery and radiation therapy may be of non-solid" and should read "example, surgery and radiation therapy may be more appropriate in the case of solid well-defined tumor masses and less practical in the case of non-solid".

The published version of the application, page 6, column 1, line 28, reads "ATGGACTCTGCAGCGTTGTC; (SEQ ID NO: 29)" and should read "ATGGACTCTCCAGCGTTCTC; (SEQ ID NO: 29)".

The published version of the application, page 6, column 1, line 30, reads "ATCGACTCTCGAGCGTTCTG; (SEQ ID NO: 31)" and should read "ATCGACTCTCGAGCGTTCTC; (SEQ ID NO: 31)".

The published version of the application, page 6, column 1, line 39, reads "TCCATGTGGCTCCTGATGCT; (SEQ ID NO: 40)" and should read "TCCATGTCGCTCCTGATGCT; (SEQ ID NO: 40)".

The published version of the application, page 6, column 2, line 25, reads "TCGTCGCTGTCTCCCCTCTT; (SEQ ID NO: 64)" and should read "TCGTCGCTGTCTCCCCTTCTT; (SEQ ID NO: 64)".

The published version of the application, page 7, column 1, line 29, reads "GAGAAGGGGGGACCTTCGAT; (SEQ ID NO: 106)" and should read "GAGAAGGGGGGACCTTCCAT; (SEQ ID NO: 106)".

The published version of the application, page 7, column 2, line 6, reads "TGCATGTGGGTGGGGATGCT; (SEQ ID NO: 121)" and should read "TCCATGTGGGTGGGGATGCT; (SEQ ID NO: 121)".

The published version of the application, page 7, column 2, line 12, reads "TCCATGGGGTCCCTGATGGT; (SEQ ID NO: 127)" and should read "TCCATGGGGTCCCTGATGCT; (SEQ ID NO: 127)".

Applicant files this request within two months of publication, and submits that errors in the specification constitute material error and that the error occurred through no fault of the Applicant. Accordingly, no fee is enclosed.

A prompt and favorable response is earnestly solicited.

Respectfully submitted,

By: Pat LH Waller

Patrick R.H. Waller, Reg. No.: 41,418
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

Docket No.: C1037.70052US00
Date: November 9, 2006
x11/21/06x

IMMUNOSTIMULATORY NUCLEIC ACIDS AND CANCER MEDICAMENT COMBINATION THERAPY FOR THE TREATMENT OF CANCER

RELATED APPLICATIONS

[0001] This application claims priority to and is a continuation of co-pending U.S. Ser. No. 09/800,266 filed on Mar. 5, 2001, which claims priority under Title 35 §119(e) of the U.S. Provisional Application No. 60/187,214, filed Mar. 3, 2000, and entitled "Immunostimulatory Nucleic Acids and Cancer Medicament Combination Therapy for the Treatment of Cancer", the entire contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to the use of immunostimulatory nucleic acids in combination with cancer medicaments in the treatment of cancer.

BACKGROUND OF THE INVENTION

[0003] Cancer is the second leading cause of death, resulting in one out of every four deaths, in the United States. In 1997, the estimated total number of new diagnoses for lung, breast, prostate, colorectal and ovarian cancer was approximately two million. Due to the ever increasing aging population in the United States, it is reasonable to expect that rates of cancer incidence will continue to grow.

[0004] Cancer is a disease which involves the uncontrolled growth (i.e., division) of cells. Some of the known mechanisms which contribute to the uncontrolled proliferation of cancer cells include growth factor independence, failure to detect genomic mutation, and inappropriate cell signaling. The ability of cancer cells to ignore normal growth controls may result in an increased rate of proliferation. Although the causes of cancer have not been firmly established, there are some factors known to contribute, or at least predispose a subject, to cancer. Such factors include particular genetic mutations (e.g., BRCA gene mutation for breast cancer, APC for colon cancer), exposure to suspected cancer-causing agents, or carcinogens (e.g., asbestos, UV radiation) and familial disposition for particular cancers such as breast cancer.

[0005] Cancer is currently treated using a variety of modalities including surgery, radiation therapy and chemotherapy. The choice of treatment modality will depend upon the type, location and dissemination of the cancer. For example, surgery and radiation therapy may be of non-solid tumor cancers such as leukemia and lymphoma. One of the advantages of surgery and radiation therapy is the ability to control to some extent the impact of the therapy, and thus to limit the toxicity to normal tissues in the body. However, surgery and radiation therapy are often followed by chemotherapy to guard against any remaining or radio-resistant cancer cells. Chemotherapy is also the most appropriate treatment for disseminated cancers such as leukemia and lymphoma as well as metastases.

[0006] Chemotherapy refers to therapy using chemical and/or biological agents to attack cancer cells. Unlike localized surgery or radiation, chemotherapy is generally administered in a systemic fashion and thus toxicity to normal tissues is a major concern. Because many chemotherapy agents target cancer cells based on their proliferative profiles, tissues such as the gastrointestinal tract and the bone marrow which are normally proliferative are also susceptible to the effects of the chemotherapy. One of the major side effects of chemotherapy is myelosuppression (including anemia, neutropenia and thrombocytopenia) which results from the death of normal hemopoietic precursors.

[0007] Many chemotherapeutic agents have been developed for the treatment of cancer. Not all tumors, however, respond to chemotherapeutic agents and others although initially responsive to chemotherapeutic agents may develop resistance. As a result, the search for effective anti-cancer drugs has intensified in an effort to find even more effective agents with less non-specific toxicity.

[0008] Recently, it has been shown that nucleic acid molecules having a CpG dinucleotide motif in which the C is unmethylated are also useful in the prevention and treatment of cancer (U.S. Pat. No. 6,194,388). These nucleic acid molecules are believed to stimulate innate immune responses against cancer cells, as well as acting as adjuvants for the induction of specific immune responses to cancer cells.

SUMMARY OF THE INVENTION

[0009] The invention provides improved methods and products for the treatment of subjects having cancer or at risk of developing cancer. The invention is based, in part, on the finding that when some types of immunostimulatory nucleic acid molecules are used in conjunction with some forms of cancer medicament, some unexpected and improved results are observed. For instance, the efficacy of the combination of some immunostimulatory nucleic acids and some cancer medicaments is profoundly improved over the use of the cancer medicament alone. The results are surprising, in part, because the immunostimulatory nucleic acids and the cancer medicaments act through different mechanisms and would not necessarily be expected to improve the efficacy of the other in a synergistic manner.

[0010] In one aspect, the invention provides a method for treating a subject having, or at risk of developing, a cancer, comprising administering to a subject in need of such treatment a poly-G nucleic acid and a cancer medicament in an effective amount to treat the cancer or to reduce the risk of developing the cancer. The poly-G nucleic acid is not conjugated to the cancer medicament.

[0011] In certain embodiments of some aspects of the invention, unless otherwise indicated, the cancer medicament embraces at least one or more chemotherapeutic agents, immunotherapeutic agents, cancer vaccines, biological response modifiers (e.g., cytokines and hemopoietic growth factors), or hormone therapies (e.g., adrenocorticosteroids, androgens, anti-androgens, estrogens, anti-estrogens, progestins, aromatase inhibitor, gonadotropin-releasing hormone agonists, and somatostatin analogs).

[0012] In one embodiment, the cancer medicament is a chemotherapeutic agent selected from the group consisting of methotrexate, vincristine, adriamycin, cisplatin, non-sugar containing chloroethylnitrosoureas, 5-fluorouracil, mitomycin C, bleomycin, doxorubicin, dacarbazine, taxol, fragyline, Meglamine GLA, valrubicin, carmustaine and poliferposan, MM1270, BAY 12-9566, RAS famesyl trans-

more appropriate in the case of solid well-defined tumor masses and less practical in the case

TABLE 1-continued

GCTAGACGTTAGCGT;	(SEQ ID NO: 4)
GCATGACGTTGAGCT;	(SEQ ID NO: 5)
ATGGAAGGTCCAGCGTTCTC;	(SEQ ID NO: 6)
ATCGACTCTCGAGCGTTCTC;	(SEQ ID NO: 7)
ATCGACTCTCGAGCGTTCTC;	(SEQ ID NO: 8)
ATCGACTCTCGAGCGTTCTC;	(SEQ ID NO: 9)
ATGGAAGGTCCAACGTTCTC;	(SEQ ID NO: 10)
GAGAACGCTGGACCTTCCAT;	(SEQ ID NO: 11)
GAGAACGCTCGACCTTCCAT;	(SEQ ID NO: 12)
GAGAACGCTCGACCTTCGAT;	(SEQ ID NO: 13)
GAGAACGCTGGACCTTCCAT;	(SEQ ID NO: 14)
GAGAACGATGGACCTTCCAT;	(SEQ ID NO: 15)
GAGAACGCTCCAGCACTGAT;	(SEQ ID NO: 16)
TCCATGTCGGTCCTGATGCT;	(SEQ ID NO: 17)
TCCATGTCGGTCCTGATGCT;	(SEQ ID NO: 18)
TCCATGACGTTCCTGATGCT;	(SEQ ID NO: 19)
TCCATGTCGGTCCTGCTGAT;	(SEQ ID NO: 20)
TCAACGTT;	(SEQ ID NO: 21)
TCAGCGCT;	(SEQ ID NO: 22)
TCATCGAT;	(SEQ ID NO: 23)
TCTTCGAA;	(SEQ ID NO: 24)
CAACGTT;	(SEQ ID NO: 25)
CCAACGTT;	(SEQ ID NO: 26)
AACGTTCT;	(SEQ ID NO: 27)
TCAACGTC;	(SEQ ID NO: 28)
ATGGACTCTCCAGCGTTCTC;	(SEQ ID NO: 29)
ATGGAAGGTCCAACGTTCTC;	(SEQ ID NO: 30)
ATCGACTCTCGAGCGTTCTC;	(SEQ ID NO: 31)
ATGGAGGCTCCATCGTTCTC;	(SEQ ID NO: 32)
ATCGACTCTCGAGCGTTCTC;	(SEQ ID NO: 33)
ATCGACTCTCGAGCGTTCTC;	(SEQ ID NO: 34)
TCCATGTCGGTCCTGATGCT;	(SEQ ID NO: 35)
TCCATGCCGGTCCTGATGCT;	(SEQ ID NO: 36)
TCCATGGCGGTCCTGATGCT;	(SEQ ID NO: 37)
TCCATGACGGTCCTGATGCT;	(SEQ ID NO: 38)
TCCATGTCGATCCTGATGCT;	(SEQ ID NO: 39)
TCCATGTCGCTCCTGATGCT;	(SEQ ID NO: 40)
TCCATGTCGTCCCTGATGCT;	(SEQ ID NO: 41)

TABLE 1-continued

TCCATGACGTGCCTGATGCT;	(SEQ ID NO: 42)
TCCATAACGTTCCTGATGCT;	(SEQ ID NO: 43)
TCCATGACGTCCCTGATGCT;	(SEQ ID NO: 44)
TCCATCACGTGCCTGATGCT;	(SEQ ID NO: 45)
GGGGTCAACGTTGACGGGG;	(SEQ ID NO: 46)
GGGGTCAGTCGTGACGGGG;	(SEQ ID NO: 47)
GCTAGACGTTAGTGT;	(SEQ ID NO: 48)
TCCATGTCGTTCCTGATGCT;	(SEQ ID NO: 49)
ACCATGGACGATCTGTTTCCCCTC;	(SEQ ID NO: 50)
TCTCCCAGCGTGCGCCAT;	(SEQ ID NO: 51)
ACCATGGACGAACTGTTTCCCCTC;	(SEQ ID NO: 52)
ACCATGGACGAGCTGTTTCCCCTC;	(SEQ ID NO: 53)
ACCATGGACGACCTGTTTCCCCTC;	(SEQ ID NO: 54)
ACCATGGACGTACTGTTTCCCCTC;	(SEQ ID NO: 55)
ACCATGGACGGTCTGTTTCCCCTC;	(SEQ ID NO: 56)
ACCATGGACGTTCTGTTTCCCCTC;	(SEQ ID NO: 57)
CACGTTGAGGGGCAT;	(SEQ ID NO: 58)
TCAGCGTGCGCC;	(SEQ ID NO: 59)
ATGACGTTCCTGACGTT;	(SEQ ID NO: 60)
TCTCCCAGCGGGCGCAT;	(SEQ ID NO: 61)
TCCATGTCGTTCCTGTCGTT;	(SEQ ID NO: 62)
TCCATAGCGTTCCTAGCGTT;	(SEQ ID NO: 63)
TCGTCGCTGTCTCCCCTCTT;	(SEQ ID NO: 64)
TCCTGACGTTCCTGACGTT;	(SEQ ID NO: 65)
TCCTGTCGTTCCTGTCGTT;	(SEQ ID NO: 66)
TCCATGTCGTTTTTGTCGTT;	(SEQ ID NO: 67)
TCCTGTCGTTCCTTGTCGTT;	(SEQ ID NO: 68)
TCCTTGTCGTTCCTGTCGTT;	(SEQ ID NO: 69)
TCCTGTCGTTTTTTGTCGTT;	(SEQ ID NO: 70)
TCGTCGCTGTCTGCCCTTCTT;	(SEQ ID NO: 71)
TCGTCGCTGTTGTCGTTTCTT;	(SEQ ID NO: 72)
TCCATGCGTGCGTGCGTTTT;	(SEQ ID NO: 73)
TCCATGCGTTGCGTTGCGTT;	(SEQ ID NO: 74)
TCCACGACGTTTTCGACGTT;	(SEQ ID NO: 75)
TCGTCGTTGTCGTTGTCGTT;	(SEQ ID NO: 76)
TCGTCGTTTTGTCGTTTTGTCGTT;	(SEQ ID NO: 77)
TCGTCGTTGTCGTTTTGTCGTT;	(SEQ ID NO: 78)
GCGTGCGTTGTCGTTGTCGTT;	(SEQ ID NO: 79)

TABLE 1-continued

TGTCGTTTGTCGTTTGTCGTT;	(SEQ ID NO: 80)
TGTCGTTGTCGTTGTCGTTGTCGTT;	(SEQ ID NO: 81)
TGTCGTTGTCGTTGTCGTT;	(SEQ ID NO: 82)
TCGTCGTCGTCGTT;	(SEQ ID NO: 83)
TGTCGTTGTCGTT;	(SEQ ID NO: 84)
TCCATAGCGTTCCTAGCGTT;	(SEQ ID NO: 85)
TCCATGACGTTCCTGACGTT;	(SEQ ID NO: 86)
GTCGYT;	(SEQ ID NO: 87)
TGTCGYT;	(SEQ ID NO: 88)
AGCTATGACGTTCCAAGG;	(SEQ ID NO: 89)
TCCATGACGTTCCTGACGTT;	(SEQ ID NO: 90)
ATCGACTCTCGAACGTTCTC;	(SEQ ID NO: 91)
TCCATGTCGGTCCTGACGCA;	(SEQ ID NO: 92)
TCTTCGAT;	(SEQ ID NO: 93)
ATAGGAGGTCCAACGTTCTC;	(SEQ ID NO: 94)
GCTAGAGGGGAGGGT;	(SEQ ID NO: 95)
GCTAGATGTTAGGGG;	(SEQ ID NO: 96)
GCTAGAGGGGAGGGT;	(SEQ ID NO: 97)
GCTAGAGGGGAGGGT;	(SEQ ID NO: 98)
GCATGAGGGGGAGCT;	(SEQ ID NO: 99)
ATGGAAGGTCCAGGGGGCTC;	(SEQ ID NO: 100)
ATGGACTCTGGAGGGGGCTC;	(SEQ ID NO: 101)
ATGGACTCTGGAGGGGGCTC;	(SEQ ID NO: 102)
ATGGACTCTGGAGGGGGCTC;	(SEQ ID NO: 103)
ATGGAAGGTCCAAGGGGCTC;	(SEQ ID NO: 104)
GAGAAGGGGGGACCTTCCAT;	(SEQ ID NO: 105)
GAGAAGGGGGGACCTTCCAT;	(SEQ ID NO: 106)
GAGAAGGGGGGACCTTGGAT;	(SEQ ID NO: 107)
GAGAAGGGGGGACCTTCCAT;	(SEQ ID NO: 108)
GAGAAGGGGGGACCTTCCAT;	(SEQ ID NO: 109)
GAGAAGGGGCCAGCACTGAT;	(SEQ ID NO: 110)
TCCATGTGGGGCCTGATGCT;	(SEQ ID NO: 111)
TCCATGTGGGGCCTGATGCT;	(SEQ ID NO: 112)
TCCATGAGGGGCCTGATGCT;	(SEQ ID NO: 113)
TCCATGTGGGGCCTGCTGAT;	(SEQ ID NO: 114)
ATGGACTCTCCGGGGTTCTC;	(SEQ ID NO: 115)
ATGGAAGGTCCGGGGTTCTC;	(SEQ ID NO: 116)
ATGGACTCTGGAGGGGTCTC;	(SEQ ID NO: 117)

TABLE 1-continued

ATGGAGGCTCCATGGGGCTC;	(SEQ ID NO: 118)
ATGGACTCTGGGGGGTTCTC;	(SEQ ID NO: 119)
ATGGACTCTGGGGGGTTCTC;	(SEQ ID NO: 120)
TCCATGTGGGTGGGGATGCT;	(SEQ ID NO: 121)
TCCATGCGGGTGGGGATGCT;	(SEQ ID NO: 122)
TCCATGGGGGTCCTGATGCT;	(SEQ ID NO: 123)
TCCATGGGGGTCCTGATGCT;	(SEQ ID NO: 124)
TCCATGTGGGGCCTGATGCT;	(SEQ ID NO: 125)
TCCATGTGGGGCCTGATGCT;	(SEQ ID NO: 126)
TCCATGGGGTCCCTGATGCT;	(SEQ ID NO: 127)
TCCATGGGGTGCCTGATGCT;	(SEQ ID NO: 128)
TCCATGGGGTTCCTGATGCT;	(SEQ ID NO: 129)
TCCATGGGGTCCCTGATGCT;	(SEQ ID NO: 130)
TCCATCGGGGGCCTGATGCT;	(SEQ ID NO: 131)
GCTAGAGGGAGTGT;	(SEQ ID NO: 132)
GGGGGGGGGGGGGGGGGGGG;	(SEQ ID NO: 133)
ACTGACAGACTGACAGACTGA;	(SEQ ID NO: 134)
AGTGACAGACAGACACACTGA;	(SEQ ID NO: 135)
ACTGACAGACTGATAGACCCA;	(SEQ ID NO: 136)
AGTGAGAGACTGCAAGACTGA;	(SEQ ID NO: 137)
AATGCCAGTCCGACAGGCTGA;	(SEQ ID NO: 138)
CCAGAACAGAAGCAATGGATG;	(SEQ ID NO: 139)
CCTGAACAGAAGCCATGGATG;	(SEQ ID NO: 140)
GCAGAACAGAAGACATGGATG;	(SEQ ID NO: 141)
CCACAACACAAGCAATGGATA;	(SEQ ID NO: 142)
AAGCTAGCCAGCTAGCTAGCA;	(SEQ ID NO: 143)
CAGCTAGCCACCTAGCTAGCA;	(SEQ ID NO: 144)
AAGCTAGGCAGCTAACTAGCA;	(SEQ ID NO: 145)
GAGCTAGCAAGCTAGCTAGGA;	(SEQ ID NO: 146)

[0053] Nucleic acids having modified backbones, such as phosphorothioate backbones, also fall within the class of immunostimulatory nucleic acids. U.S. Pat. Nos. 5,723,335 and 5,663,153 issued to Hutcherson, et al. and related PCT publication WO95/26204 describe immune stimulation using phosphorothioate oligonucleotide analogues. These patents describe the ability of the phosphorothioate backbone to stimulate an immune response in a non-sequence specific manner. Thus some embodiments of the invention rely on the use of phosphorothioate backbone nucleic acids which lack CpG, poly-G and T-rich motifs.

[0054] In the case when the immunostimulatory nucleic acid is administered in conjunction with a nucleic acid